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(54) Title: MICRO–OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

(57) Abstract

Disclosed herein are compositions and methods related to pharmaceutical compositions that employ a micro–osmotic core for the controlled delivery of a therapeutic agent. The invention particularly relates to therapeutic agents which are present in some portion in a solid state solution in the composition.

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MICRO-OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

BACKGROUND OF THE INVENTION

The invention relates to the field of osmotic release systems for the controlled release of a therapeutic agent. Osmotic release systems facilitate the controlled release of a medicament from a dosage form based on a change in osmotic pressure in the dosage form. Osmotic release systems are useful for the delivery of both poorly soluble and highly soluble therapeutic agents.

SUMMARY OF THE INVENTION

In accordance with the current invention, a micro-osmotic controlled drug delivery system has been developed. The micro-osmotic system contains the following components: a micro-osmotic core, a drug component, and, optionally, a controlled release matrix and/or coating.

The micro-osmotic core contains at least one osmotic agent and, optionally, a swelling agent and/or a gelling agent. Osmotic agents facilitate the penetration of aqueous biological fluids into the micro-osmotic core. Osmotic agents include, for example, sorbitol, mannitol, xylitol, sodium chloride or any other such highly soluble and pharmaceutically acceptable excipient. Preferred osmotic agents include, for example, the following osmotic agents: spray dried sorbitol, particularly Sorbitol Instant (EM Industries, Hawthorne, New York), which has a surface area of ~1m^2/g; spray dried mannitol; mannitol with a polymorphic composition (dry state) that contains not less than about 85% of the "δ" form of mannitol; a combination of sorbitol-mannitol-xylitol, preferably with sorbitol ≥ 90%, mannitol ≥ 4%, and xylitol ≥4%, such as described in DE 196 47 282 A1, P96 47 282 - DE and WO 44 39 858, PCT/EP95/04059.

The micro-osmotic core may also optionally comprise a swelling agent. The swelling agent expands in volume when contacted by aqueous biological fluids, thereby changing the volume of the micro-osmotic core. A swelling agent preferably is capable

of swelling to a volume that is many times its volume in the dry state. Preferred swelling agents include, for example, sodium starch glycollate, crosscarmellose sodium, cellulose, and microcrystalline cellulose.

The micro-osmotic core may also optionally comprise a gelling agent. The gelling agent functions to maintain the integrity of the swelling agent and thereby functions to maintain the integrity of the micro-osmotic core. The gelling agent is preferably a water soluble polymer. Preferred gelling agents include, for example, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP) and its derivatives, gums - tragacanth, accacia, guar, carageenan, and other carbohydrate derived gums, alginic acid and its derivatives, and carbomers.

The micro-osmotic core is in the form of small particles, with diameter ranges of between about 2 μm to about 3000 μm, preferably 200 μm about to about 3000 μm, and more preferably about 200 μm to about 1500 μm. The particles may be miniature tablets such as, for example, may be formed using a water soluble lubricant such as PEG 8000. The micro-osmotic core may also be extruded and spheronized into small spheres and/ or spray agglomerated into particles. The osmotic agent/swelling agent/gelling agent may be combined in weight ratios ranging from 100/0/0 to 0.05/99.9/0.05 to 99.9/0.05/0.05 to 0.05/0.05/99.9. Preferred ratios of osmotic agent/swelling agent/gelling agent are the following: 1/8/1, 2/7/1, 3/6/1, 4/5/1, 6/2/2, 7/1/2, 8/1/1, 9/0.5/0.5, and 5/4/1.

The micro-osmotic cores of the invention are coated with a drug component to obtain loaded cores. Coated, as used herein, refers to any physical contact between the drug component and the micro-osmotic core. For example, micro-osmotic cores may be fully coated with the drug component, partially coated with the drug component, or impregnated with the drug component. Loaded cores preferably have diameter ranges of between about 2 μm to about 3000 μm, more preferably about 200 μm to about 3000 μm, and most preferably about 200 μm to about 1500 μm. The drug component comprises at least one therapeutic agent. The therapeutic agent in the drug component may be, for example, in the form of a solid, a solid-state solution, a solid-state solution-dispersion, a

microdisperse system, a solution-suspension (e.g. aqueous, alcoholic, or hydroalcoholic), or any combination thereof. The therapeutic agents may be combined with select excipients and/or binders. The solution-suspension form of the therapeutic agent may optionally include a hydrophilic agent such as HPMC, HPC, PVP, sorbitol, and/or natural gums (for example, accacia) in addition to water, alcohol, or a hydroalcoholic system.

A solid-state solution, as used herein, refers to a solution of the therapeutic agent in solid form. A solid-state solution of the therapeutic agent is characterized by the lack of a melting point peak at the melting point of the therapeutic agent, indicating the absence of the solid state of the therapeutic agent. A solid state solution-dispersion, as used herein, is a system in which part of the therapeutic agent is in the form of a solid-state solution and part of the therapeutic agent is in the form of a finely dispersed solid. Preferably, greater than 1% of the total therapeutic agent content exists in solution in the system, in either the solid, semi-solid, or liquid phases. The system is also characterized in that at least one therapeutic agent can exist as a solid dispersion. Any portion of the therapeutic agent which exists as a solid dispersion preferably has a particle size distribution wherein the diameter of about 90% of the particles is less than about 10μ.

For a solid-state solution-dispersion, the solubilized therapeutic agent/dispersed therapeutic agent ratio is in a range from 1/99 to 100/0. Preferably, about 30% to about 100% of the therapeutic agent exists in solution, and more preferably, about 60% to about 90% of the therapeutic agent exists in solution. The ratio of the amount of therapeutic agent present in the form of a solid-state solution to the amount present in the form of solid dispersion can be easily ascertained by the use of techniques in thermal analysis such as Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), and Differential Scanning Microcalorimetry. The crystallinity of the therapeutic agent is easily determined by X-ray diffraction.

One example of a solid-state solution-dispersion system, particularly for therapeutic agents having poor water solubility, comprises a mixture of saturated polyglycolyzed glycerides (for example, Gelucire®, available from Gattefosse),

polyoxypropylene-polyoxyethylene block copolymer (for example, Pluronic®NF surfactants, available from BASF), and a therapeutic agent, as described, for example, in U.S. Patent Application No. 09/050913 and in U.S. Provisional Patent Application Nos. 60/080163, 60/085417,60/085333, and 60/092767. The polyglycolyzed glycerides component of the pharmaceutical carrier composition may include all grades of the saturated and unsaturated polyglycolyzed glycerides, preferably polyglycolyzed glycerides with a hydrophilic-lipophilic balance (HLB) > 10. Preferred polyglycolyzed glycerides include, for example, Gelucire ® 44/13 and Gelucire ® 50/13. The mixture may also include all grades of polyoxypropylene-polyoxyethylene block co-polymer, preferably polyoxypropylene-polyoxyethylene block co-polymers with a HLB > 10. Preferred polyoxypropylene-polyoxyethylene block co-polymers include, for example, Pluronic® L44, Pluronic® F68, Pluronic® F108, and Pluronic® F127. The polyglycolyzed glycerides/polyoxypropylene-polyoxyethylene block co-polymer may be combined in weight ratios ranging from about 0.10/99.9 to about 99.9/0.10. The preferred ratios are 1/9, 2/8, 3/7, 4/6, 6/4, 7/3, 8/2, 9/1 and 5/5. The combination of saturated polyglycolyzed glycerides/polyoxypropylene-polyoxyethylene block co-polymer preferably has a melting point in the range of about 30°C to about 70°C, and more preferably about 50°C to about 70°C. When a polyglycolyzed glycerides/polyoxypropylene-polyoxyethylene block co-polymer combination is employed, the combination is present in the final composition of the drug component in an amount of about 0.10% to about 99.9%, and preferably about 5% to about 75%. Therapeutic agents are present in the final composition of the drug component in an amount of about 0.10% to about 99.9%, preferably about 5% to about 75%.

Examples of therapeutic agents that may be used in conjunction with this invention include the following: dihydropyridine compounds, including for example, nifedepine, felodipine, nicardipine; cyclopeptides, including for example cyclosporine; omperazol; spironolactone; furosemide; terbutaline; riboflavin; gemfibrozi; indomethacin; ibuprofen; phenytoin; and glyburide. Additionally, any therapeutic agent with an intrinsic solubility of less than about 10.0 g/L and having therapeutic

activity in any of the following areas are contemplated as part of this invention: activity in the cardiovascular system; immunosuppressive activity; cholesterol lowering activity; anti-hypertensive activity; anti-epileptic activity; hormonal activity; hypoglycemic activity; anti-viral activity; anti-histaminic activity; nasal decongestant activity; anti-microbial activity; anti-arrthrytic activity; analgesic activity, anti-mycobacterial, anti-cancer activity, diuretic activity, anti-fungal activity, anti-parasitic activity, activity as a central nervous system (CNS) stimulant, activity as a CNS depressant, activity as a 5-HT inhibitor, anti-schizophrenia activity, anti-alzheimer activity, anti-psoriatic activity, anti-ulcer activity, activity as a proton pump inhibitor, anti-asthmatic activity, activity as a bronchodialator, and thrombolytic activity. The therapeutic agent may be, for example, a protein, a peptide, a cyclopeptide, a steroid molecule, a vitamin, an oligonucleotide, or any small or large molecule, or any combination of the foregoing.

In addition to the therapeutic agent or agents, the drug component may optionally comprise excipients. Excipients preferably comprise about 5% to about 95% by weight of the final composition of the drug component, and more preferably about 10% to about 70%. Examples of suitable excipients include, but are not limited to, the following: ascorbyl palmitate; tocopheryl acetate; glycerol; glyceryl monooleate; glyceryl monosterate; glyceryl palmitosterate; triglycerides; diglycerides; monoglycerides; stearic acid; magnesium stearate, talc, diesters of polyethylene glycol (PEG); monoesters of PEG; polyethylene glycol; glyceryl polyoxyethylene fatty acid esters; glyceryl polyoxyethylene polyethylene glycol fatty acid esters and ethers; polyoxyethylene alkyl ethers; polyoxyethylene castor oil derivatives; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene sterates; polyvinyl alcohol; sodium starch glycollate; sorbitan fatty acid esters; polyoxyl sterates; polyethylene glycol hydroxysterate; polyoxyethylene alcohols; anionic; cationic; amphiphilic compounds; lecithins; phospholipids; carbohydrates, including for example, lactose, maltodextrins, sucrose, and starch; polyols, including for example, sorbitol, mannitol, and xylitol; microcrystalline cellulose; vitamins, including for example, ascorbic acid and

niacinamide; bioflavonoids, including for example, quercetin, isoquercetin, naringin, rutin, etc.; and inorganic compounds, including for example, calcium carbonate, dicalcium phosphate, and any combinations of the above mentioned materials.

The micro-osmotic cores that are coated with a drug component (loaded cores), can be either coated with a suitable polymeric coating and/or combined with a polymer matrix system. The polymer coating or the polymer matrix may serve to modify the release profile of the therapeutic agent from the loaded cores. The polymer coating may comprise, for example, the following: hydrophilic polymers such as, for example HPMC, HPC, derivatives of cellulose, derivatives of starch, PVP and PVP derivatives, and carbomers; water insoluble polymers such as, for example, ethyl cellulose, cellulose acetate, polymethacrylate polymers (for example, Eudragit® polymers,) and pseudolatex dispersions of the above; enteric polymers such as, for example, shellac, cellulose acetate phthalate; plasticizers such as, for example, dibutyl sebecate, triacetin, acetyl tributyl phthalate; and pearlescent pigments such as, for example, the Candurin™ line of pigments (EM Industries, Hawthorne, New York). Coating of the loaded cores can be performed using pharmaceutical techniques that are well known in the art, including techniques such as wurster coating, rotor coating, and/or pan coating.

The polymer matrix comprises at least one hydrophilic polymer such as, for example, cellulose and its derivatives, including, for example, HPMC, HEC, Carbomers (e.g. Carbopol P934, Carbopol P974), and alginic acid and its derivatives. The hydrophilic polymers of the polymer matrix preferably have molecular weights of between about 100 to about 4,000,000. The hydrophilic polymers are also preferably combined with at least one hydration enhancer which allows for faster hydration of the hydrophilic polymer. Hydration enhancers include, for example, sorbitol, mannitol, xylitol, and microcrystalline cellulose, and any combination thereof. A preferred hydrating enhancer is a specialized spray agglomerated form of sorbitol (commercially available as Sorbitol Instant, EM Industries, Hawthorne, New York) which has a surface area of $1 m^2/g$. Hydrophilic polymers of different molecular weights and different

chemical natures may be combined to achieve the desired release profile for the therapeutic agent.

The loaded cores and the polymer matrix may be dry blended and then granulated by using a suitable solvent (e.g. aqueous and/or organic) and/or processed to form beads or spheres, or compressed into tablets using suitable lubricants. Suitable lubricants for compressing the dry blended mixture of the loaded cores and the polymer matrix include, for example, sodium stearyl fumarate, magnesium sterate, PEG 8000. A flow promoter such as, colloidal silicon dioxide, may also be employed as part of the compression step.

The product from the above processes, which comprises loaded cores, both coated and uncoated, optionally blended with a polymeric matrix to form a dry blend, and optionally further processed to form granules, beads, spheres or tablets, may be further processed into final dosage forms as follows. As one example, granules, spheres, beads or the dry blend may be compressed into tablets, and the tablets may optionally be coated with a polymeric coating to modify the release profile of the therapeutic agent. The polymeric coating is essentially as described above. As another example, beads, spheres, or granules may be coated with a polymeric coating essentially as described above. The coated beads, spheres or granules may then be encapsulated into capsules or compressed into tablets, with the use of suitable pharmaceutical excipients.

It is also contemplated as part of this invention that a final dosage form may comprise more than one type of loaded core. For example, loaded cores containing same therapeutic agent but having different release profiles may be incorporated into the final dosage formulation. Different release profiles for loaded cores containing the same therapeutic agent may be obtained, for example, by varying the content of the micro-osmotic core or the polymeric coating of the loaded cored. Alternatively, loaded cores having different therapeutic agents may also be incorporated into the same final dosage formulation.

The invention also relates to a method of manufacturing a pharmaceutical composition. The method comprises the steps of providing a micro-osmotic core,

coating the micro-osmotic core with a drug component to form loaded cores, and optionally, formulating the loaded cores into final dosage forms as described above.

The invention also relates to a method for delivering one or more therapeutic agents to a physiologic target site. The method comprises the steps of providing a pharmaceutical composition according to the invention and introducing a pharmaceutically effective amount of the pharmaceutical composition to a physiologic target site. The introduction of the pharmaceutical composition to the physiologic target site may be accomplished, for example, by administration topically, subcutaneously, intramuscularly, intraperitoneally, nasally, pulmonarily, vaginally, rectally, aurally, orally or ocularly. A preferred method for delivering at least one therapeutic agent to a physiologic target site that is contemplated by this invention is through oral delivery.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the *in vitro* release profile of felodipine from tablets formed according to example 17.

Figure 2 is a graph showing the *in vitro* release profile of felodipine from tablets formed according to example 18.

Figure 3 is a graph showing the *in vitro* release profile of felodipine from tablets formed according to example 19.

Figure 4 is a graph showing the *in vitro* release profile of felodipine from tablets formed according to example 20.

Figure 5 is a graph showing the *in vitro* release profile of felodipine from tablets formed according to example 21.

Figure 6 is a graph showing the *in vitro* release profile of felodipine from tablets formed according to example 22.

Figure 7 is a graph showing the *in vitro* release profile of felodipine from tablets formed according to example 23.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure.

EXAMPLES

In the following examples, all parts and percentages are by weight unless otherwise indicated.

For examples 17-23 below, the following components were employed.

1. Pruv™ - (sodium stearyl fumarate) (available from Mendell).
2. Avicel™ PH200 - (microcrystalline cellulose NF) (available from FMC).
3. Sorbitol Instant P300 - (Sorbitol NF) (available from Merck KGaA).
4. Methocel™ E4M Premium CR - (hydroxypropylmethyl cellulose NF) (available from Dow Chemical).
5. Methocel™ K100 M - (hydroxypropylmethyl cellulose NF) (available from Dow Chemical).
6. Triacetin™ - (glyceroltriacetate) (available from Spectrum Quality Products).
7. Eudragit® NE 30 D - (30% aqueous dispersion of polyacrylate copolymers) (available from Roehm).
8. Eudragit® L 30 D - (30% aqueous dispersion of methacrylic acid/methacrylate copolymers) (available from Roehm).
9. PVP 30 - (polyvinylpyrrolidone, MW: 44,000-54,000) (available as Kollidon® 30 from BASF)
10. Gelucire® 50/13 - (saturated polyglycolized glycerides of hydrogenated vegetable oil consisting glycerides and PEG-esters) (available from Gattefosse).
11. Pluronic® F 68 - (polyoxy propylene-polyoxy ethylene block copolymers) (available from BASF)

Example 1: Manufacture of the micro-osmotic cores.

Micro-osmotic cores may be manufactured by any number of techniques known in the art, using a variety of materials. A few of these techniques and materials are as follows:

(1) crystalline or spray agglomerated sorbitol are employed as the micro-osmotic core;

(2) sorbitol, sodium starch glycollate, and HPMC are combined and compressed into miniature tablets (for example, a diameter < 1 mm) using PEG 8000 as a lubricant;

(3) sorbitol powder and sodium starch glycollate are combined, and the mixture is extruded and spheronized into spheres;

(4) sodium starch glycollate is spray agglomerated onto sorbitol.

Micro-osmotic cores may be made using any of the above methods or using any other techniques that are well known in the art, including granulation.

Example 2: Manufacture of the therapeutic agent component as a solid state solution-dispersion.

A mixture of polyglycolyzed glycerides and polyoxypropylene-polyoxyethylene block copolymer are heated to 20°C above the melting point (~50°C). The therapeutic agent is added gradually to the molten mixture. The therapeutic agent is preferably milled to a particle size range such that the diameter of at least about 90% of the particles is less than about 75 microns. The mixture is maintained at 20°C above the melting point of the polyglycolyzed glycerides/polyoxypropylene-polyoxyethylene block co-polymer mixture. The ratio of the polyglycolyzed glycerides/polyoxypropylene-polyoxyethylene block co-polymer is selected to facilitate solubilization of > 1% and preferably 30-100% of the therapeutic agent in the mixture.

Example 3: Controlled release tablets containing Nifedepine.

	Ingredients:	Quantities (mg/Tab):	Application
1.	Sorbitol Instant P300	50	osmotic core
2.	Nifedepine, USP	90	active

3.	Gelucire 50/13	90	excipient
4.	Pluronic F68	90	excipient
5.	HPMC E4M CR Grade	300	hydrophillic polymer
6.	Sorbitol Instant P300	75	hydration enhancer
7.	Microcrystalline Cellulose	75	hydration enhancer
8.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant was used as an osmotic core. Gelucire 50/13, Pluronic F68, and Nifedepine were processed together to yield a drug component having Nifedepine as the therapeutic agent in a solid state solution-dispersion. The drug component was then spray congealed onto Sorbitol Instant. The loaded cores as manufactured above were blended with a polymeric matrix containing Sorbitol Instant P300, HPMC E4M CR Grade, microcrystalline cellulose, and magnesium stearate. Controlled release tablets were obtained by compression of the mixture of the loaded cores with the polymeric formulation.

Example 4: Controlled release tablets containing Felodipine.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	Felodipine, USP	90	active
4.	Gelucire 50/13	90	excipient
5.	Pluronic F68	90	excipient
6.	HPMC E4M CR Grade	300	hydrophillic polymer
7.	Sorbitol Instant P300	75	hydration enhancer
8.	Microcrystalline Cellulose	75	hydration enhancer
9.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300 and sodium starch glycollate were combined into a micro-osmotic core. Gelucire 50/13, Pluronic F68, and felodipine were combined to yield drug component having felodipine in a solid-state solution. The drug component was then spray congealed onto the micro-osmotic core. The loaded cores as manufactured above were then blended with Sorbitol Instant P300, HPMC E4M CR Grade, microcrystalline cellulose, and magnesium stearate. Controlled release tablets were obtained by compression of the mixture of the loaded cores with the polymeric formulation.

Example 5: Controlled release tablets containing Phenytoin.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	HPMC E4M	10	gelling agent
4.	Phenytoin, USP	95	active
5.	Gelucire 50/13	90	excipient
6.	Pluronic F68	90	excipient
7.	HPMC K100 Grade	300	hydrophillic polymer
8.	Sorbitol Instant P300	150	hydration enhancer
9.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300, HPMC E4M and sodium starch glycollate are processed together into a micro-osmotic core. Gelucire 50/13, Pluronic F68, and Phenytoin are processed together to yield a solid state solution of Phenytoin in the matrix. This drug system is spray congealed onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC E4M CR Grade, microcrystalline cellulose, and magnesium stearate. Controlled release tablets are compressed with the above formulation.

Example 6: Controlled release tablets containing indomethacin.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	HPMC E4M	10	gelling agent
4.	Indomethacin, USP	100	active
5.	PVP	90	excipient, binder
6.	HPMC K100 Grade	300	hydrophillic polymer
7.	Sorbitol Instant P300	150	hydration enhancer
8.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300, HPMC E4M and sodium starch glycollate are processed together into a micro-osmotic core. PVP, and Indomethacin are processed together to yield a suspension in ethanol. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC E4M CR Grade, microcrystalline cellulose, and magnesium stearate. Controlled release tablets are compressed with the above formulation.

Example 7: Controlled release tablets containing Chlorpheniramine maleate.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	HPMC E4M	10	gelling agent
4.	Chlorpheniramine maleate	10	active
5.	PVP	20	excipient, binder
6	HPMC K100 Grade	300	hydrophillic polymer
7.	Sorbitol Instant P300	150	hydration enhancer
8.	Microcrystalline Stearate	6.8	lubricant

Sorbitol Instant P300, HPMC E4M and sodium starch glycollate are processed together into a micro-osmotic core. PVP and chlorpheniramine maleate are processed together to yield a solution in water. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC E4M CR Grade, microcrystalline cellulose, and magnesium stearate. Controlled release tablets are compressed with the above formulation.

Example 8: Controlled release tablets containing Diltiazem hydrochloride.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	160	osmotic agent
2.	Sodium starch glycollate	40	swelling agent
3.	HPMC E4M	20	gelling agent
4.	Diltiazem hydrochloride	300	active
5.	PVP	60	excipient, binder
6	Ethyl Cellulose dispersion	q.s.	hydrophobic polymer
7.	Dibutyl sebecate	q.s.	plasticizer
8.	Talc	q.s.	anti-caking agent

Sorbitol Instant P300, HPMC E4M and sodium starch glycollate are processed together into a micro-osmotic core. PVP and diltiazem hydrochloride are processed together to yield a solution in water. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are coated with ethyl cellulose dispersion plasticized with dibutyl sebecate. Controlled release tablets are compressed with the above formulation.

Example 9: Capsules containing controlled release pellets containing Chlorpheniramine maleate.

Ingredients:	Quantities (mg/Tab):	Application:

1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	PVP	10	gelling agent
4.	Chlorpheniramine maleate	10	active
5.	PVP	20	excipient, binder
6	Eudragit RS 30D dispersion	q.s.	hydrophobic polymer
7.	Dibutyl sebacate	q.s.	plasticizer
8.	Talc	q.s.	anti-caking agent

Sorbitol Instant P300, HPMC E4M and sodium starch glycollate are processed together into a micro-osmotic core. PVP and chlorpheniramine maleate are processed together to yield a solution in water. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are coated with Eudragit RS 30D (polymethacrylate copolymer) dispersion plasticized with dibutyl sebecate. Controlled release pellets are encapsulated into capsules.

Example 10: Controlled release tablets containing Nifedepine.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	HPMC E4M	10	gelling agent
4.	Nifedepine, USP	90	active
5.	PVP	90	excipient, binder
6	Locust bean gum	175	hydrophillic polymer
7.	Xanthan Gum	175	hydrophillic polymer
8.	Sorbitol Instant P300	150	hydration enhancer
9.	Calcium Chloride	25	crosslinking agent
10.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300, HPMC E4M and sodium starch glycollate are processed together into a micro-osmotic core. PVP and Nifedepine are processed together to yield a suspension in ethanol. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, locust bean gum, Xanthan gum, calcium chloride, and finally with magnesium stearate. Controlled release tablets are compressed with the above formulation.

Example 11: Controlled release tablets containing Nifedepine.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	Nifedepine, USP	90	active
4.	PVP	90	excipient, binder
5.	HPMC K100 Grade	300	hydrophillic polymer
6.	Sorbitol Instant P300	150	hydration enhancer
7.	Ethyl cellulose	100	hydrophobic polymer
8.	Triacetin	25	plasticizer
9.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300 and sodium starch glycollate are processed together into a micro-osmotic core. PVP and Nifedepine are processed together to yield a suspension in ethanol. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade and granulated with a granulating solvent composed of ethyl cellulose and Triacetin, dried, delumped and finally combined with magnesium stearate. Controlled release tablets are compressed with the above formulation.

Example 12: Controlled release tablets containing Nifedepine.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	Nifedepine, USP	90	active
4.	PVP	90	excipient, binder
5.	HPMC K100 Grade	300	hydrophillic polymer
6.	Sorbitol Instant P300	150	hydration enhancer
7.	Ethyl cellulose	100	hydrophobic polymer
8.	Triacetin	25	plasticizer
9.	HPMC E4M	10	hydrophillic polymer
10	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300 and sodium starch glycollate are processed together into a micro-osmotic core. PVP and Nifedepine are processed together to yield a suspension in ethanol. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade and granulated with a granulating solvent composed of ethyl cellulose, HPMC E4M, and triacetin, dried, delumped and finally combined with magnesium stearate. Controlled release tablets are compressed with the above formulation.

Example 13: Controlled release tablets containing Nifedepine.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	Nifedepine, USP	90	active
4.	PVP	90	excipient, binder
5.	HPMC K100 Grade	300	hydrophillic polymer
6.	Sorbitol Instant P300	150	hydration enhancer

7.	Ethyl cellulose	100	hydrophobic polymer
8.	Triacetin	25	plasticizer
9.	HPMC E4M	10	hydrophillic polymer
10.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300 and sodium starch glycollate are processed together into a micro-osmotic core. PVP and Nifedepine are processed together to yield a suspension in ethanol. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade and granulated with a granulating solvent composed of ethyl cellulose and triacetin, dried, delumped and finally combined with magnesium stearate. Controlled release tablets are compressed with the above formulation. These tablets are coated with a semi-permeable polymer coating system composed of ethyl cellulose, HPMC E4M, and triacetin.

Example 14: Controlled release tablets containing Nifedepine.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	50	osmotic agent
2.	Sodium starch glycollate	20	swelling agent
3.	Nifedepine, USP	90	active
4.	PVP	90	excipient, binder
5.	HPMC K100 Grade	300	hydrophillic polymer
6.	Sorbitol Instant P300	150	hydration enhancer
7.	Eudragit NE 30D	100	hydrophobic polymer
8.	Dibutyl sebecate	25	plasticizer
9.	HPMC E4M	10	hydrophillic polymer
10.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300 and sodium starch glycollate are processed together into a micro-osmotic core. PVP and Nifedepine are processed together to yield a suspension in ethanol. This drug system is spray coated onto the micro-osmotic core. The drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade and granulated with a granulating solvent composed of Eudragit NE 30D (polymethacrylate copolymer dispersion) and triacetin, dried, delumped and finally combined with magnesium stearate. Controlled release tablets are compressed with the above formulation. These tablets are coated with a semi-permeable polymer coating system composed of Eudragit NE 30D (polymethacrylate copolymer dispersion), HPMC E4M and Triacetin.

Example 15: Controlled release tablets containing Verapamil hydrochloride.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	220	osmotic agent
2.	Sodium starch glycollate	40	swelling agent
3.	Verapamil hydrochloride	240	active
4.	PVP	60	excipient, binder
5.	HPMC K100 Grade	300	hydrophillic polymer
6.	Sorbitol Instant P300	50	hydration enhancer
7.	Eudragit NE 30D	150	hydrophobic polymer
8.	Eudragit L30D	100	hydrophobic polymer
9	Dibutyl sebecate	75	plasticizer
10.	HPMC E4M	10	hydrophillic polymer
11.	Magnesium Stearate	6.8	lubricant

Sorbitol Instant P300 and sodium starch glycollate are combined to form a micro-osmotic core. PVP and verapamil hydrochloride are processed together to yield a solution in water. This drug system is spray coated onto the micro-osmotic core. The drug micro-osmotic cores are divided in two portions. One portion of the drug system

micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade and granulated with a granulating solvent composed of Eudragit NE 30D (polymethacrylate copolymer dispersion) and triacetin, dried, and delumped. One portion of the drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade and granulated with a granulating solvent composed of Eudragit L 30D (polymethacrylate copolymer dispersion) and triacetin, dried, and delumped. Material obtained in steps c and d are combined, blended with magnesium stearate. Controlled Release Tablets are compressed with the above formulation. These tablets are coated with a semi-permeable polymer coating system composed of Eudragit NE 30D (polymethacrylate copolymer dispersion), HPMC E4M, and triacetin.

Example 16: Capsules containing Verapamil hydrochloride.

	Ingredients:	Quantities (mg/Tab):	Application:
1.	Sorbitol Instant P300	220	osmotic agent
2.	Sodium starch glycollate	40	swelling agent
3.	Verapamil hydrochloride	240	active
4.	PVP	6	excipient, binder
5.	HPMC K100 Grade	300	hydrophillic polymer
6.	Sorbitol Instant P300	50	hydration enhancer
7.	Eudragit NE 30D	100	hydrophobic polymer
8.	Eudragit L30D	150	hydrophobic polymer
9.	Dibutyl sebecate	75	plasticizer
10.	Talc	q.s.	anti-caking agent

Sorbitol Instant P300 and sodium starch glycollate are processed together into a micro-osmotic core. PVP and verapamil hydrochloride are processed together to yield a solution in water. This drug system is spray coated onto the micro-osmotic core. The drug micro-osmotic cores are divided into two portions. One portion of the drug system

micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade and granulated with a granulating solvent composed of Eudragit NE 30D (polymethacrylate copolymer dispersion) and triacetin, dried, and delumped. These granules are then coated with Eudragit L30D (polymethacrylate copolymer) system plasticized with dibutyl sebecate. One portion of the drug system micro-osmotic cores as manufactured above are blended with Sorbitol Instant P300, HPMC K100 Grade, pelletized and granulated with a granulating solvent composed of Eudragit L 30D (polymethacrylate copolymer dispersion) and triacetin, dried, and delumped. Material obtained in steps c and d are combined, blended with talc and encapsulated into capsules.

For examples 17-23 below, the following Felodipine Matrix component was employed:

Felodipine USP	1.5 g
Gelucire 50/13	1.5 g
Pluronic F 68	1.5 g
Sorbitol Instant P300	4.0g

The Gelucire and Pluronic were melted together. Felodipine was dissolved in the mixture, and the solution was added to Sorbitol Instant P300 while stirring. The mixture was mixed well and allowed to congeal. The congealed mixture was then passed through a # 20 mesh.

Example 17: *In vitro* release profile of felodipine tablets having a micro-osmotic core.

Excipients	mg/tablet	Supplier
HPMC E4M	112.5	Dow Chemical
Sorbitol P300	66	EMI
Avicel PH200	209.48	FMC

Felodipine Matrix	60.98	EMI
Pruv	1	Mendell

The HPMC, Sorbitol Instant, Avicel and the Felodipine Matrix were combined. Pruv was added to the mixture and the mixture was mixed well. Samples of the mixture (450 mg) were compressed into a tablet using Carver Press, with compression at 2 Ton. Each tablet was placed in a basket and the *in vitro* release profile was measured in a 900 ml solution of 1% sodium lauryl sulfate in deionized water, with paddle agitation at 50 rpm. Samples of the solution were taken at different time points and the absorbence at 362 nm was measured. The results of the measurements are presented in the tables below and in Figure 1.

Time (h)	$t^{1/2}$	% release	s.d.
0	0	0	
2	1.41421356	20.43	3.07
4	2	38.56	3.24
6	2.44948974	55.3	3.03
8	2.82842712	70.51	4.22
10	3.16227766	86.79	6.54
12	3.46410162	95.24	1.4

According to the Higuchi Equation: $\%=Kt^{1/2}$ + constant:

Tablet	r	slope	intercept
felodipine	0.9739667	28.60726	-10.1986

According to the Zero Order Release:

Tablet	r	slope	intercept
felodipine	0.9952701	8.042679	4.148214

Example 18: *In vitro* release profile of felodipine tablets having a micro-osmotic core.

Excipients	mg/tablet	Supplier
HPMC E4M Premium CR	112.5	Dow Chemical
Sorbitol P300	67.5	EMI
Avicel PH200	212.3	FMC
Felodipine Matrix	56.7	EMI
Pruv	1	Mendell

The procedures were the same as described for Example 17 above. The results of the measurements are presented in the tables below and in Figure 2.

Time (h)	$t^{1/2}$	7-8 KP % release	s.d.	6-7 KP % released	s.d.
0	0	0	0	0	0
2	1.41	66.59	13.5	59.88	5.33
4	2	88.9	8.13	85.88	2.27
6	2.45	95.87	2.88	99.47	2.57
8	2.83	97.79	3.64	102.06	3.38
10	3.16	97.46	3.08	101.72	3.42
12	3.46				

According to the Higuchi Equation: $\%=Kt^{1/2}$ + constant:

Tablet	r	slope	intercept
7-8 KP	0.98997	40.6174942	3.335371
6-7 KP	0.99881	41.2926417	0.81378

According to the Zero Order Release:

Tablet	r	slope	intercept
7-8 KP	0.91526	15.496	16.352
6-7 KP	0.95079	16.2205	12.646

Example 19: *In vitro* release profile of felodipine tablets.

Excipients	mg/tablet	Supplier
E4M & K100M formulation:		
HPMC E4M	106.88	Dow Chemical
HPMC K100M	5.62	Dow Chemical
Sorbitol P300	73.39	EMI
Avicel PH200	227.76	FMC
Felodipine Matrix	30.36	EMI
Pruv	.99	Mendell

E4M formulation:

HPMC E4M	112.5	Dow Chemical
Sorbitol P300	73.39	EMI
Avicel PH200	227.76	FMC
Felodipine Matrix	30.36	EMI
Pruv	.99	Mendell

The HPMCs, Sorbitol Instant, Avicel and the Hydrosolve-Felodipine component were combined. Pruv was added to the mixture and the mixture was mixed well. Samples of the mixture (445 mg) were compressed into tablets using a Carver Press, with compression at 2 Ton. Each tablet was placed in a basket and the in vitro release profile was measured in a 900 ml solution of 1% sodium lauryl sulfate in deionized water, with paddle agitation at 50 rpm. Samples of the solution were taken at different time points and the absorbence at 362 nm was measured. The results of the measurements are presented in the tables below and in Figure 3.

Time (h)	$t^{1/2}$	95% E4M &	K100 M	100% E4M	
		% released	s.d	% released	s.d.
0	0	0	0	0	0
2	1.41	14.63	2.13	15.99	6.15
4	2	41.5	3.86	42.52	7.24
6	2.45	63.26	6.21	64.29	5.4
8	2.83	75.85	6.79	78.23	5.23
10	3.16	90.14	6.24	88.78	4.66
12	3.46	96.6	6.56	95.92	3.06

According to the Higuchi Equation: $\%=Kt^{1/2}$ + constant:

Tablet	r	slope	intercept
E4M & K100M	0.95949	29.55133836	-10.80056
E4M	0.96362	29.5771156	-10.11314

According to the Zero Order Release:

Tablet	r	slope	intercept
E4M & K100M	0.99329	10.1065	-1.018

E4M	0.99509	10.238	-0.746

Example 20: *In vitro* release profile of felodipine tablets.

Excipients	mg/tablet	Supplier
HPMC E4M	101.25	Dow Chemical
HPMC K100M	11.25	Dow Chemical
Sorbitol P300	73.39	EMI
Avicel PH200	227.76	FMC
Felodipine Matrix	30.36	EMI
Pruv	.99	Mendell

The HPMCs, Sorbitol Instant, Avicel and the Hydrosolve-Felodipine component were combined. Pruv was added to the mixture and the mixture was mixed well. Samples of the mixture (445 mg) were compressed into tablets using a Carver Press, with compression at 2 Ton. Each tablet was placed in a basket and the in vitro release profile was measured in a 900 ml solution of 1% sodium lauryl sulfate in deionized water, with paddle agitation at 50 rpm. Samples of the solution were taken at different time points and the absorbence at 362 nm was measured. The results of the measurements are presented in the tables below and in Figure 4.

Time (h)	$t^{1/2}$	HydroSolve % release	s.d.
0	0	0	
2	1.41	19.6	3.54
4	2	36.96	2.46
6	2.45	54.39	0
8	2.83	68.86	0.62

10	3.16	79.83	3.73
12	3.46	89.04	10.54

According to the Higuchi Equation: $\%=Kt^{1/2}$ + constant:

Tablet	r	slope	intercept
felodipine	0.9779732566	26.8444051	-8.90112

According to the Zero Order Release:

Tablet	r	slope	intercept	t_{90}
felodipine	0.9922566	7.49071429	4.8671429	11.3651187

Example 21: *In vitro* release profile of felodipine tablets.

Excipients	mg/tablet	Supplier

K100M formulation:

HPMC K100M	50.75	Dow Chemical
Sorbitol P300	33.2	EMI
Avicel PH200	103.3	FMC
Felodipine Matrix	15.18	EMI
Pruv	.45	Mendell

E4M & K100M formulation:

HPMC E4M	40.6	Dow Chemical
HPMC K100M	10.15	Dow Chemical
Sorbitol P300	33.2	EMI
Avicel PH200	103.3	FMC
Felodipine Matrix	15.18	EMI
Pruv	.45	Mendell

The HPMCs, Sorbitol Instant, Avicel and the Hydrosolve-Felodipine component were combined. Pruv was added to the mixture and the mixture was mixed well. Samples of the mixture (203 mg) were compressed into tablets using a Carver Press, with compression at 2 Ton. Each tablet was placed in a basket and the in vitro release profile was measured in a 900 ml solution of 1% sodium lauryl sulfate in deionized water, with paddle agitation at 50 rpm. Samples of the solution were taken at different time points and the absorbence at 362 nm was measured. The results of the measurements are presented in the tables below and in Figure 5.

Time (h)	$t^{1/2}$	K100M		E4M & K100M	
		% release	s.d	% released	s.d.
0	0	0	0	0	0
2	1.41421	15.82	2.59	18.64	2.94
4	2	34.46	2.59	46.89	7.64
6	2.44949	57.63	10.31	71.75	5.45
8	2.82843	72.32	9.79	86.44	7.38
10	3.16228	79.82	10.66	89.83	11.11

According to the Higuchi Equation: $\%=Kt^{1/2}$ + constant:

Tablet	r	slope	intercept
K100M	0.9598	26.6965209	-9.402476
E4M & K100M	0.9655	31.1539762	-9.293658

According to the Zero Order Release:

Tablet	r	slope	intercept
K100M	0/9977	9.3225	-1.244

E4M & K100M	0.9953	11.2995	-0.454

Example 22: *In vitro* release profile of tablets made from hydrosolve.

Formula I (10% Sorbitol)

Excipients	mg/tablet	Supplier
HPMC E4M	50.75	Dow Chemical
Sorbitol P300	33.2	EMI
Avicel PH200	103.3	FMC
Felodipine Matrix	15.18	EMI
Pruv	0.45	Mendell

The HPMCs, Sorbitol Instant, Avicel and the Hydrosolve-Felodipine component were combined. Pruv was added to the mixture and the mixture was mixed well. Samples of the mixture (203 mg) were compressed into tablets using a Carver Press, with compression at 2 Ton. Each tablet was placed in a basket and the in vitro release profile was measured in a 900 ml solution of 1% sodium lauryl sulfate in deionized water, with paddle agitation at 50 rpm. Samples of the solution were taken at different time points and the absorbence at 362 nm was measured. The results of the measurements are presented in the tables below and in Figure 6.

Time (h)	$t^{1/2}$	HydroSolve % release	s.d.
0	0	0	0
2	1.414213562	53.41	3.89
4	2	85.31	6.06
6	2.449489743	98.33	1.76
8	2.828427125	101.75	1.76
9	3	101.75	1.76

10	3.15227766		

According to the Higuchi Equation: $\%=Kt^{1/2}$ + constant:

Tablet	r	slope	intercept
Felodipine	0.9907336	38.00593	1.6895071

According to the Zero Order Release:

Tablet	r	slope	intercept
Felodipine	0.9261162	12.421	18.076

Example 23: *In vitro* release profile of felodipine tablets.

Excipients	mg/tablet	Supplier
HPMC E4M	62.19	Dow Chemical
Sorbitol P300	30.45	EMI
Avicel PH200	94.73	FMC
Felodipine Matrix	15.18	EMI
Pruv	0.45	Mendell

The HPMCs, Sorbitol Instant, Avicel and the Hydrosolve-Felodipine component were combined. Pruv was added to the mixture and the mixture was mixed well. Samples of the mixture (203 mg) were compressed into tablets using a Carver Press, with compression at 2 Ton. Each tablet was placed in a basket and the in vitro release profile was measured in a 900 ml solution of 1% sodium lauryl sulfate in deionized water, with paddle agitation at 50 rpm. Samples of the solution were taken at different time points and the absorbence at 362 nm was measured. The results of the measurements are presented in the tables below and in Figure 7.

Time (h)	$t^{1/2}$	HydroSolve % release
0	0	0
2	1.41421356	20.27
4	2	48.65
6	2.4494897	67.12

According to the Higuchi Equation: $\%=Kt^{1/2}$ + constant:

Tablet	r	slope	intercept
Felodipine	0.9723567	31.17882739	-9.19942

According to the Zero Order Release:

Tablet	r	slope	intercept
Felodipine	0.9897404	9.729285714	3.755238

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The entire disclosure of all patent applications, patents, and publications cited herein are hereby incorporated by reference.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope

thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising

loaded cores comprising micro-osmotic cores having a coating of a drug component thereon,

wherein the micro-osmotic cores comprise at least one micro-osmotic agent and,

wherein the drug component comprises at least one therapeutic agent.

2. A pharmaceutical composition according to claim 1, wherein at least one micro-osmotic agent is sorbitol, mannitol, xylitol, or sodium chloride.

3. A pharmaceutical composition according to claim 1, wherein the micro-osmotic core further comprises at least one swelling agent or at least one gelling agent.

4. A pharmaceutical composition according to claim 1, wherein the drug component comprises at least a portion of at least one therapeutic agent in a solid-state solution.

5. A pharmaceutical composition according to claim 4, wherein the drug component comprises a polyglycolyzed glycerides component and a polyoxypropylene-polyoxyethylene block copolymer component.

6. A pharmaceutical composition according to claim 5, wherein at least portion of at least one therapeutic agent is in a solid state solution in a mixture comprising the polyglycolyzed glycerides component and the polyoxypropylene-polyoxyethylene block co-polymer component.

7. A pharmaceutical composition according to claim 6, wherein the portion of the therapeutic agent in a solid state solution comprises between 30% to 100% of the therapeutic agent in the drug component.

8. A pharmaceutical composition according to claim 6, wherein the loaded cores are coated with a polymeric coating.

9. A pharmaceutical composition according to claim 6, wherein the loaded cores are combined with a polymer matrix.

10. A pharmaceutical composition according to claim 6, wherein the loaded cores are coated with polymeric coating and combined with a polymer matrix.

11. A pharmaceutical composition according to claim 1, wherein the diameter of the loaded cores ranges from 2 μ to 3 mm.

12. A pharmaceutical composition according to claim 6, wherein the therapeutic agent is a dihydropyridine compound.

13. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of

providing a pharmaceutical composition according to claim 6; and

introducing a pharmaceutically effective amount of the pharmaceutical composition to physiologic target site.

14. A method according to claim 13, wherein the physiologic target site is the gastrointestinal tract.

15. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of

providing a pharmaceutical composition according to claim 7; and

introducing a pharmaceutically effective amount of the pharmaceutical composition to physiologic target site.

16. A method according to claim 1, wherein the physiologic target site is the gastrointestinal tract.

17. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of

providing a pharmaceutical composition according to claim 1; and

introducing a pharmaceutically effective amount of the pharmaceutical composition to physiologic target site.

18. A method of formulating a pharmaceutical composition comprising the steps of

providing a micro-osmotic core,

coating the micro-osmotic core with a drug component.

19. A method according to claim 18, wherein the drug component comprises a mixture of a polyglycolyzed glycerides component and the polyoxypropylene-polyoxyethylene block co-polymer component.

20. A method according to claim 19, wherein at least a portion of at least one therapeutic agent exists in a solid state solution in the mixture.

21. A method according to claim 20, wherein the portion of at least one therapeutic agent comprises 30% to 100%.

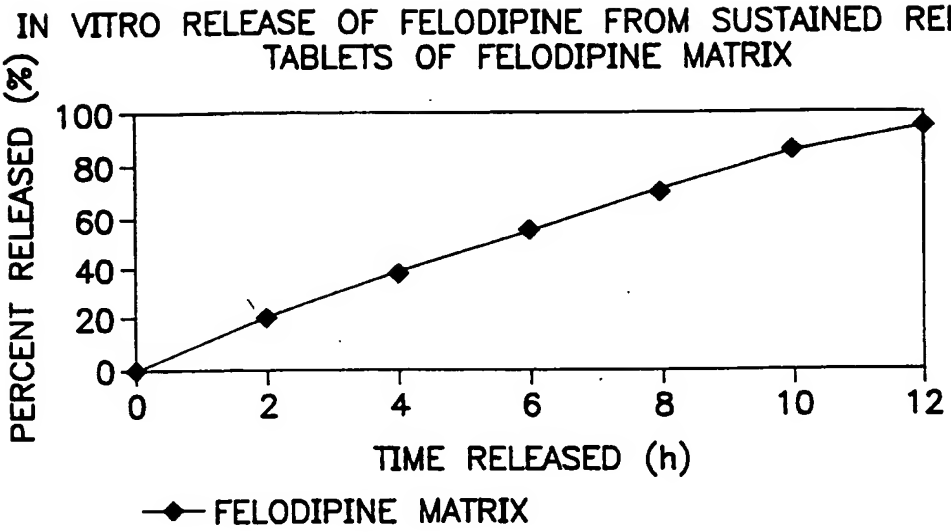
IN VITRO RELEASE OF FELODIPINE FROM SUSTAINED RELEASE TABLETS OF FELODIPINE MATRIX
PERCENT RELEASED (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
TIME RELEASED (h)
FELODIPINE MATRIX

FIG. 1

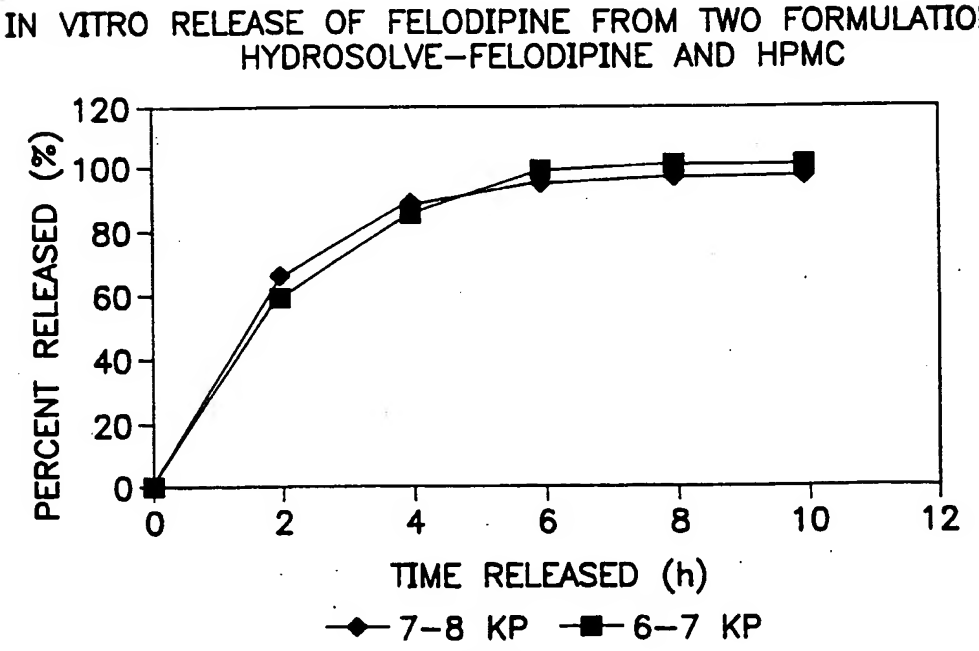
IN VITRO RELEASE OF FELODIPINE FROM TWO FORMULATIONS OF HYDROSOLVE–FELODIPINE AND HPMC
PERCENT RELEASED (%)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
TIME RELEASED (h)
7–8 KP
6–7 KP

FIG. 2

IN VITRO RELEASE OF FELODIPINE FROM TWO FORMULATIONS OF HYDROSOLVE–FELODIPINE AND HPMC

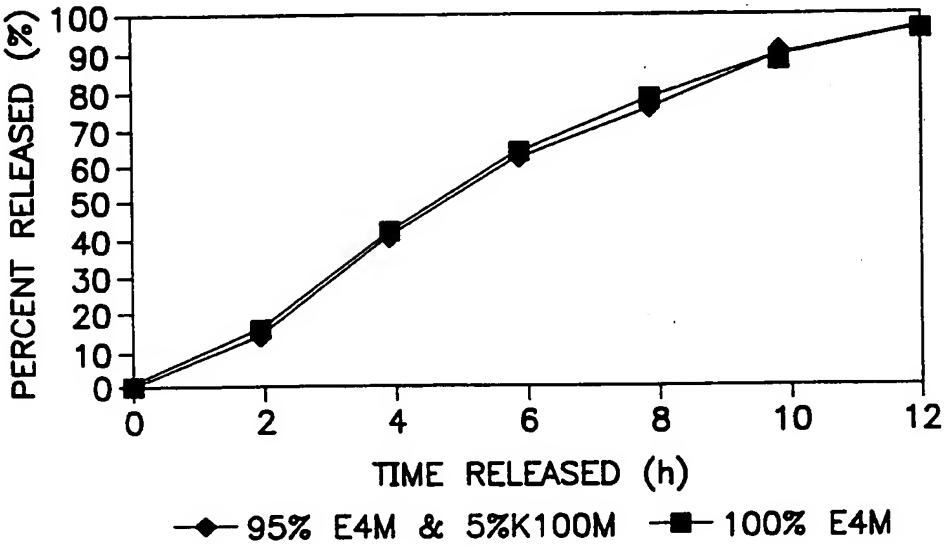

FIG. 3

COMPARISON OF IN VITRO RELEASE PROFILES OF FELODIPINE FROM HYDROSOLVE–FELODIPINE FORMULATION

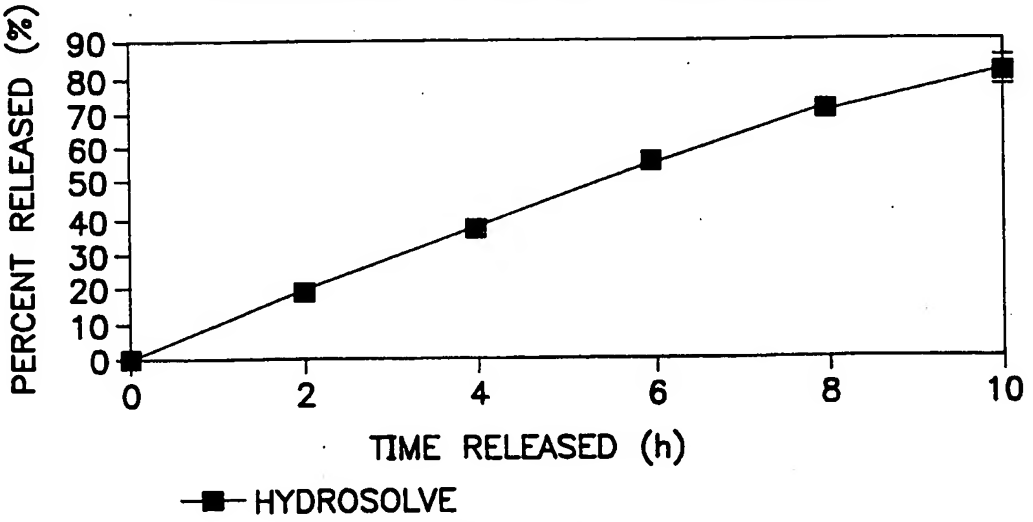

FIG. 4

IN VITRO RELEASE OF FELODIPINE FROM TWO DIFFERENT FORMULATIONS OF HYDROSOLVE–FELODIPINE WITH HPMC

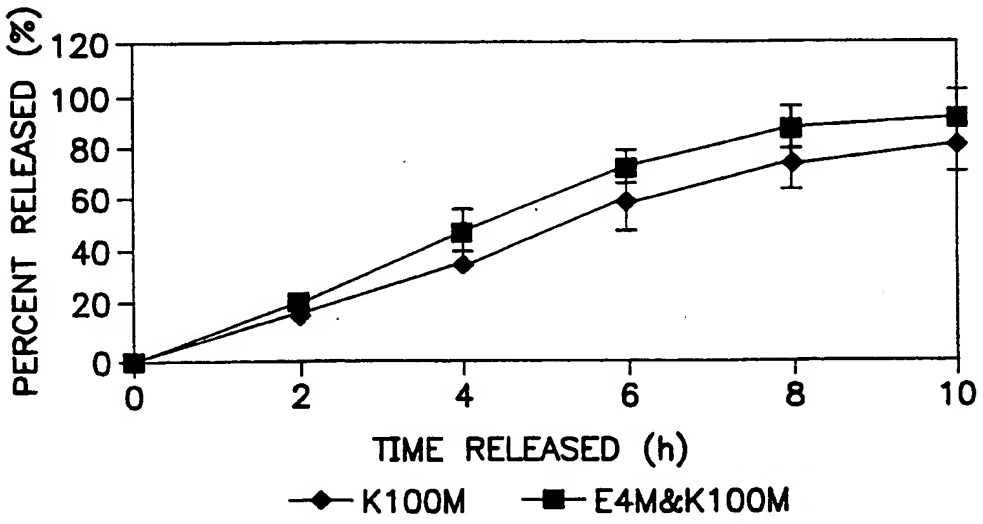

FIG. 5

IN VITRO RELEASE OF FELODIPINE FROM SUSTAINED RELEASE TABLETS OF HYDROSOLVE

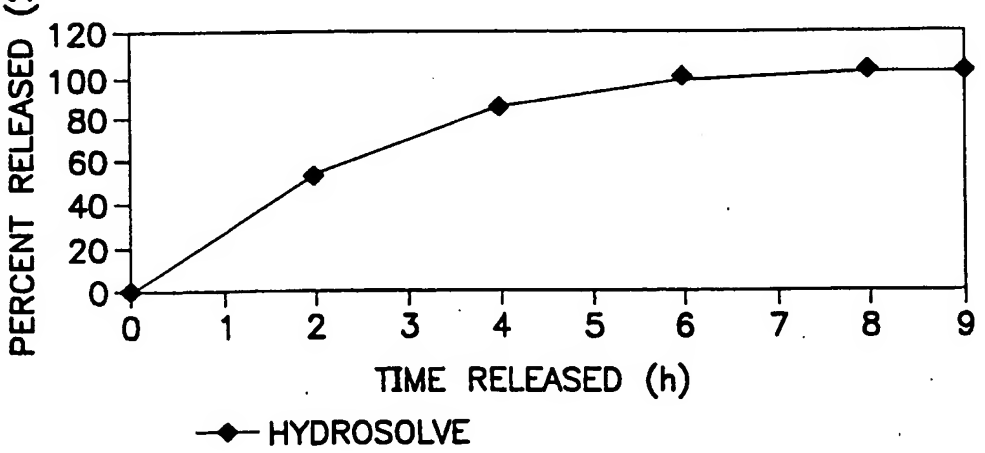

FIG. 6

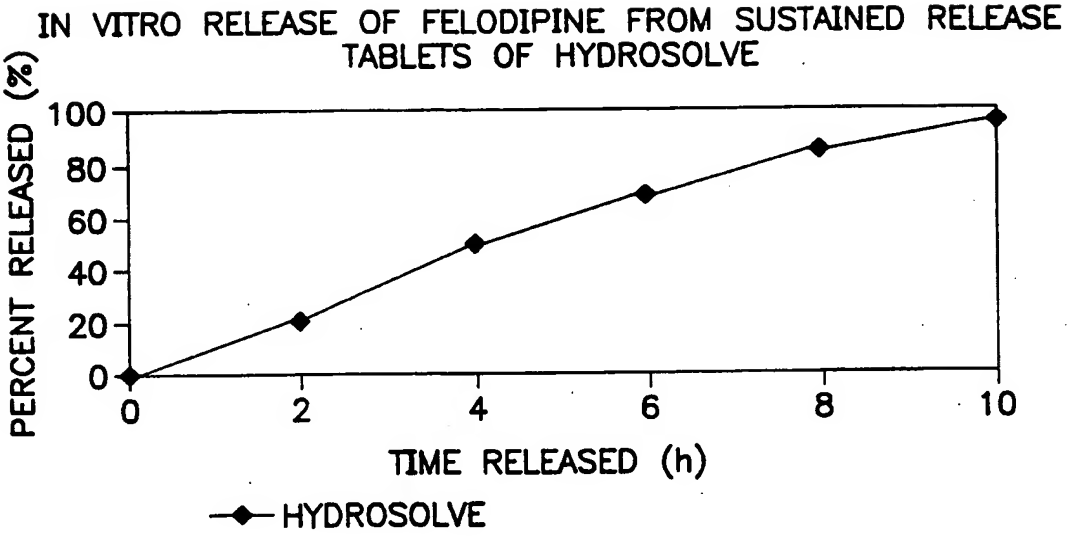
IN VITRO RELEASE OF FELODIPINE FROM SUSTAINED RELEASE TABLETS OF HYDROSOLVE
PERCENT RELEASED (%)
100
80
60
40
20
0
0
2
4
6
8
10
TIME RELEASED (h)
HYDROSOLVE

FIG. 7

INTERNATIONAL SEARCH REPORT

Int* ational Application No
PCT/US 99/13223

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 00116 A (SCHERING CORPORATION) 8 January 1998 (1998-01-08) claims 1,2,4,7-9 page 4, line 17 -page 7, line 21 ---	1-4,11, 13,14, 16-18
X	US 4 758 437 A (TAKASHI, SONOBE; ET AL.) 19 July 1988 (1988-07-19) claim 1 column 2, line 54 -column 3, line 15 ---	1,4, 11-14, 16-18
X	WO 97 02017 A (ELAN CORPORATION) 23 January 1997 (1997-01-23) claims 1,20 page 12, line 9 - line 15 --- -/--	1,4, 11-14, 16-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search .	Date of mailing of the international search report
4 October 1999	18/10/1999

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 116, no. 8, 24 February 1992 (1992-02-24) Columbus, Ohio, US; abstract no. 67105, JANICKI, S. ET AL: "Therapeutic formulation/diffusion system with a sparingly soluble drug (isosorbide dinitrate)" XP002117378 abstract & PHARMAZIE (1991), 46(7), 541-2 ,1991,	1,2,4, 11,16-18
A	US 5 260 068 A (CHIH-MING CHEN) 9 November 1993 (1993-11-09) the whole document	2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. tional Application No
PCT/US 99/13223

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9800116 A	08-01-1998	AU 3387497 A	21-01-1998
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		CZ 9804214 A	16-06-1999
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		AU 680620 B	07-08-1997
		JP 9500866 T	28-01-1997

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60/088,855 11 June 1998 (11.06.98) US

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(74) Agents: JOYCE, Catherine, M. et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza I, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

Date of publication of the amended claims:
10 February 2000 (10.02.00)

(54) Title: MICRO–OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

(57) Abstract

Disclosed herein are compositions and methods related to pharmaceutical compositions that employ a micro–osmotic core for the controlled delivery of a therapeutic agent. The invention particularly relates to therapeutic agents which are present in some portion in a solid state solution in the composition.

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AMENDED CLAIMS

[received by the International Bureau on 16 December 1999 (16.12.99);
original claims 1-21 replaced by amended claims 1-17 (3 pages)]

1. A pharmaceutical composition comprising loaded cores comprising micro-osmotic cores having a coating of a drug component thereon, wherein the micro-osmotic cores comprise at least one micro-osmotic agent, wherein the drug component comprises at least one therapeutic agent, and wherein at least a portion of at least one therapeutic agent is in a solid-state solution in a mixture comprising a polyglycolyzed glycerides component and a polyoxypropylene-polyoxyethylene block co-polymer component.

2. A pharmaceutical composition according to claim 1, wherein at least one micro-osmotic agent is sorbitol, mannitol, xylitol, or sodium chloride.

3. A pharmaceutical composition according to claim 1, wherein the micro-osmotic core further comprises at least one swelling agent or at least one gelling agent.

4. A pharmaceutical composition according to claim 1, wherein the portion of the therapeutic agent in a solid state solution comprises between 30% to 100% of the therapeutic agent in the drug component.

5. A pharmaceutical composition according to claim 1, wherein the loaded cores are coated with a polymeric coating.

6. A pharmaceutical composition according to claim 1, wherein the loaded cores are combined with a polymer matrix.

7. A pharmaceutical composition according to claim 1, wherein the loaded cores are coated with polymeric coating and combined with a polymer matrix.

8. A pharmaceutical composition according to claim 1, wherein the diameter of the loaded cores ranges from 2 μ to 3 mm.

9. A pharmaceutical composition according to claim 1, wherein the therapeutic agent is a dihydropyridine compound.

10. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of providing a pharmaceutical composition according to claim 1; and introducing a pharmaceutically effective amount of the pharmaceutical composition to the physiologic target site.

11. A method according to claim 10, wherein the physiologic target site is the gastrointestinal tract.

12. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of providing a pharmaceutical composition according to claim 2; and introducing a pharmaceutically effective amount of the pharmaceutical composition to the physiologic target site.

13. A method according to claim 12, wherein the physiologic target site is the gastrointestinal tract.

14. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of providing a pharmaceutical composition according to claim 3 and introducing a pharmaceutically effective amount of the pharmaceutical composition to the physiologic target site.

15. A method according to claim 14, wherein the physiologic target site is the gastrointestinal tract.

16. A method of formulating a pharmaceutical composition comprising the steps of providing a micro-osmotic core,
coating the micro-osmotic core with a drug component,
wherein the drug component comprises at least one therapeutic agent, wherein at least a portion of at least one therapeutic agent is in a solid-state solution in a mixture comprising a polyglycolyzed glycerides component and a polyoxypropylene-polyoxyethylene block co-polymer component.

17. A method according to claim 16, wherein the portion of at least one therapeutic agent comprises 30% to 100%.